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ORIGINAL PAPER

Irreversible linear pathways in enzymatic reactions: analytical solution using the homotopy perturbation method

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Abstract
In this work, the Homotopy Perturbation method is used for the first time to solve an irreversible linear pathway with enzyme kinetics. The enzymatic system has Michaelis–Menten kinetics and is modeled by a system of nonlinear ordinary differential equations. The analytical solution obtained with the method allow us to optimize several objectives: minimal time to reach a certain percent of final product, minimal amount of enzymes employed in the process, or even multiple objective optimization via Pareto front. We present an example to demonstrate the results.

Keywords Enzymatic kinetics · Michaelis–Menten model · Ordinary differential equations · Homotopy perturbation method · Optimization

Mathematics Subject Classification 80A30 · 92E20 · 34E10

1 Introduction

Enzyme kinetics is nowadays an emerging research field due to the incorporation of novel techniques of applied mathematics. Several problems in biology and chemistry (both theoretical and experimental) involve the solution of reaction equations, including nonlinear chemical kinetics. See the book by Rajendran et al. [1] for an excellent summary with special emphasis on the mathematical resolution.

It is well known that the rate of chemical reactions is accelerated by enzymes. In enzymatic processes, one obtains a product after a series of stages: the enzymatic mechanism, of which There are two different types: single and multiple substrate mechanisms [2]. Differential equations are used to model the enzyme kinetics. The single case is one of the most powerful kinds of kinetic reaction. Michaelis and Menten

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in 1913 were pioneers in explaining the enzyme reaction model; their model was later developed by Briggs and Haldane in 1925. They reported the free enzyme binding to the reactant, which produced an enzyme-reactant complex in the standard two-step model. Catalyzed reactions like these lead to a set of non-linear coupled differential equations.

The Michaelis–Menten (MM) model [3] assumes that the concentration of enzyme-substrate complex remains approximately constant over a considerable time interval after a short transient. This is commonly known as the quasi-steady-state approximation (QSSA). In [4], several features of QSSA are discussed: one is led to believe, along with many authors, that the standard QSSA (s–QSSA) is valid only when the enzyme concentration is small, though the range of validity of the MM region is widened. On the other hand, a number of studies considered moderate-to-large enzyme substrate ratios and found QSSA regions there too, under specific circumstances. Without any restriction on substrate enzyme ratios, the so-called total QSSA (t–QSSA) applies. Borghans et al. [5] distinguished s–QSSA from t–QSSA, and also pointed out what they called QSSA (r–QSSA), which applies when the enzyme–substrate ratio is large.

Kasserra and Laidler [6] put forward certain conditions for the applicability of QSSA and suggest that an excess of initial enzyme concentration is necessary to guarantee that the reaction follows first-order kinetics. Schnell et al. [7] have shown that the criterion for validity of the reactant stationary assumption, to study the Michaelis–Menten reaction, does not require the restrictive condition of choosing a substrate concentration that is much higher than the enzyme concentration.

Despite using the QSSA simplified model, the complexity of the ensuing system is such that the development of new mathematical techniques is essential. This problem is discussed in [2], where they use He's variational iteration method is used to give approximate and analytical solutions. In [8] and [9], they employ the Homotopy Perturbation Method (HPM) to solve the non-linear reaction equation in a 1-stage system: one substrate and one product. In [10], the authors study kinetic models of reversible enzyme reactions and compare two techniques for analytic approximate solutions of the model: the Homotopy Perturbation Method (HPM) and the Simple Iteration Method (SIM). Finally, in [11], the multistep differential transform method is first employed to solve a enzyme kinetics.

However, to the best of our knowledge, there were no analytical results available to date for an irreversible linear chain of enzymatic reactions. The objective of the present work is to obtain asymptotic approximate analytic expressions for the substrates, products, enzymes and enzyme-substrates concentrations in an n-stage system (n substrates and n products), with an unbranched scheme, by applying HPM. Following [12], we assume that the optimal profile follows a pattern matching the topology of the pathway, reflecting the fact that the enzymes are activated sequentially.

The analytic solution we obtain allows us to optimize several objectives. In the present work we deal with three cases: the minimal time required to reach a certain percent of the final product; the minimal amount of enzymes used in the process; and, finally, a multiple objective optimization is presented using the well-known Pareto front. We present an example to demonstrate the results.

2 The homotopy perturbation method

In this section, we present the homotopy perturbation method (HPM) as a tool for solving non-linear ordinary differential equations with initial conditions. The HPM was proposed first by He [13] for solving differential and integral equations, both linear and nonlinear. This method provides an approximate solution to a wide range of nonlinear problems, expressed as the summation of an infinite series. The HPM can be considered as combination of the classical perturbation technique and the well-known topological concept of homotopy [14].

Consider a general nonlinear equation in the form:

$$A(y) - f(x) = 0, \quad x \in \Omega \tag{1}$$

with boundary conditions:

$$B\left(y, \frac{\partial y}{\partial n}\right) = 0, \quad x \in \Gamma \tag{2}$$

where A is any differential operator, B a boundary operator, $f(x)$ a known analytic function and Γ the boundary of the domain Ω.

The operator A can be separated into a linear part L and a nonlinear one N, so that (1) can be rewritten as:

$$L(y) + N(y) - f(x) = 0 \tag{3}$$

The method consists in constructing a homotopy $u : \Omega \times [0, 1] \to \mathbb{R}$ satisfying:

$$\begin{aligned} H(u, p) = (1 - p)[L(u(x, p)) - L(y_0(x))] + p[L(u(x, p)) \\ + N(u(x, p)) - f(x)] = 0 \end{aligned} \tag{4}$$

or:

$$H(u, p) = L(u(x, p)) - L(y_0(x)) + pL(y_0(x)) + p[N(u(x, p)) - f(x)] = 0 \tag{5}$$

where $p \in [0, 1]$ is a homotopy parameter, $x \in \Omega$, and $y_0(x)$ is the initial approximation to the solution of Eq. (1) that satisfies the boundary conditions if any. The variation of p from 0 to 1 provides that of $u(x, p)$ from $y_0(x)$ to $y(x)$.

The HPM uses the homotopy parameter p as a "small parameter", and assumes that the solutions of Eq. (4) can be written as a power series in p:

$$u(x, p) = \sum_{i=0}^{\infty} p^i u_i(x) = u_0 + pu_1 + p^2 u_2 + p^3 u_3 + \cdots \tag{6}$$

where $u_0, u_1, u_2, \ldots$ are unknown functions to be determined. Substituting (6) into (4) and matching identical powers of p terms, provides the values of the sequence $u_0, u_1, u_2, \ldots$ iteratively. Then, When $p \to 1$, the solution of (1) is given by:

$$y(x) = \lim_{p \to 1} u(x, p) = \sum_{i=0}^{\infty} u_i(x) = u_0 + u_1 + u_2 + u_3 + \cdots \tag{7}$$

as long as the power series converges for $p \to 1$.

We are going to apply this method to solve a non-linear system of 2 ordinary differential equations with initial values.

We shall not delve into convergence issues in this work, as it is out of the scope of this work.

3 Mathematical formulation of the problem

3.1 The 1-stage system

The Michaelis–Menten mechanism is the simplest chemical network which models the formation of a product through an enzymatic catalysis of a substrate (for more details on the enzyme dynamics, see [15] or [16] and the references therein). Consider the following single enzyme reaction:

$$E + S \underset{k_{-1}}{\overset{k_1}{\longleftrightarrow}} ES \overset{k_2}{\to} E + P \tag{8}$$

where S is the substrate, P the product, E is the free enzyme and ES is the enzyme-substrate complex. In this reaction k_1, k_{-1} and k_2 are positive rate constants denoting the reaction rates of the three processes. The equation shows clearly that the substrate binding is reversible but the product release is not.

Equation (8) illustrates the Michaelis–Menten kinetics proposed in 1913 [17], in which the enzyme-substrate complex is formed after the enzyme is combined with the substrate. It means that there is an equilibrium between $[E]$, $[S]$ and $[ES]$ to produce $[P]$ and $[E]$. Schnell and Maini [18] have shown that, under the condition $[E_0] >> [S_0]$, the appropriate framework to study the Michaelis–Menten reaction (8) is the so-called reverse quasi-steady-state approximation (rQSSA) or equilibrium approximation.

The concentration of the reactants in (8) will be denoted by:

$$s = [S], \quad e = [E], \quad c = [ES], \quad p = [P] \tag{9}$$

By the law of mass action, Eq. (8) can be described in terms of a system of four non-linear ordinary differential equations (ODEs):

$$\frac{ds}{dt} = -k_1 es + k_{-1} c \tag{10}$$

$$\frac{de}{dt} = -k_1 es + (k_{-1} + k_2)c \tag{11}$$

$$\frac{dc}{dt} = k_1 es - (k_{-1} + k_2)c \tag{12}$$

$$\frac{dp}{dt} = k_2 c \tag{13}$$

with initial conditions:

$$s(0) = s_0, \quad e(0) = e_0, \quad c(0) = 0, \quad p(0) = 0 \tag{14}$$

Adding Eqs. (11) and (12), it is evident that:

$$\frac{de}{dt} + \frac{dc}{dt} = 0;\ e(0) = e_0, \quad c(0) = 0 \tag{15}$$

from where:

$$e(t) + c(t) = e_0 \tag{16}$$

Using this relation, the system of four ODEs can be reduced to just three:

$$\frac{ds}{dt} = -k_1 e_0 s + (k_1 s + k_{-1})c \tag{17}$$

$$\frac{dc}{dt} = k_1 e_0 s - (k_1 s + k_{-1} + k_2)c \tag{18}$$

$$\frac{dp}{dt} = k_2 c \tag{19}$$

with initial conditions:

$$s(0) = s_0, \quad c(0) = 0, \quad p(0) = 0 \tag{20}$$

Notice that the product p can be easily obtained from c using (19), so that the third equation is actually uncoupled.

Introduce the auxiliary parameters:

$$u(\tau) = \frac{s(t)}{s_0};\ v(\tau) = \frac{c(t)}{e_0};\ w(\tau) = \frac{p(t)}{e_0} \tag{21}$$

$$\tau = \frac{k_1 e_0 t}{\varepsilon};\ \lambda = \frac{k_2}{k_1 s_0};\ \kappa = \frac{k_{-1} + k_2}{k_1 s_0};\ \varepsilon = \frac{e_0}{s_0} \tag{22}$$

where $K_S = k_{-1}/k_1$ is called the equilibrium dissociation constant, $K = k_2/k_1$ is called the Van Slyke–Cullen constant, and K_M, given by:

$$K_M = K_S + K = \frac{k_{-1} + k_2}{k_1} = \frac{\kappa}{s_0} \tag{23}$$

is know as the Michaelis–Menten constant. Using these parameters (21) and (22), the system (17), (18), and (19) can be represented in dimensionless form as follows:

$$\frac{du}{d\tau} = -\varepsilon u + \varepsilon(u + \kappa - \lambda)v;\ u(0) = 1 \tag{24}$$

$$\frac{dv}{d\tau} = u - (u + \kappa)v;\ v(0) = 0 \tag{25}$$

$$\frac{dw}{d\tau} = \lambda v;\ w(0) = 0 \tag{26}$$

where ε, κ, and λ are now dimensionless parameters. This is the system of non-linear equations which we are going to solve analytically in a simple and closed form using the Homotopy Perturbation Method (HPM). Actually, as (26) is uncoupled, we are going to solve the system given by (24) and (25).

3.2 The *n*-stage system

Now we state the problem of an unbranched metabolic pathway composed of n irreversible reactions converting an initial substrate S_1 into the product P. We have not found this type of problem analytically solved in the literature; only in some cases like [19], the authors use commercial software like Mathematica™ to compute approximate solutions to the ODEs which describe them.

Let $s_1(t)$ denote the substrate concentration at time t, $p(t)$ the concentration of the final product, $s_i(t)$, $(i = 2, \ldots, n)$ the concentration of the intermediate compounds, and $e_i(t)$, $(i = 1, \ldots, n)$ the concentration of the enzyme catalyzing the ith reaction.

$$S_1 \overset{E_1}{\rightarrow} S_2 \overset{E_2}{\rightarrow} S_3 \overset{E_3}{\rightarrow} \cdots \rightarrow S_{n-1} \overset{E_{n-1}}{\rightarrow} S_n \overset{E_n}{\rightarrow} P \tag{27}$$

Each of these stages comprises a reaction equation of the form (8), so that there are $c_i(t)$, $(i = 1, \ldots, n)$ enzyme-substrate complexes.

The optimal profile follows a pattern matching the topology of the pathway (27), reflecting the fact that the enzymes are activated sequentially; this implies that there exist n times: $t_1, t_2, ..., t_n$, as many as enzymes (we set $t_0 = 0$ and $t_n = t_f$).

Denote by $u_{ji}(\tau)$, $v_{ji}(\tau)$ and $w_{ji}(\tau)$ (for $i, j = 1, \ldots, n$) the optimal jth concentration, in the ith interval $[\tau_{i-1}, \tau_i]$ of the dimensionless parameters $u(\tau)$, $v(\tau)$ and $w(\tau)$ respectively. Following reasoning like the one in the previous section, derived from (24), (25) and (26), it is easy to obtain the following sequence of systems of differential equations (one for each interval):

(1) Interval: $[0, \tau_1]$.

$$\begin{cases} \dot{u}_1 = -\varepsilon_1 u_1 + \varepsilon_1(u_1 + \kappa_1 - \lambda_1)v_1 & u_1(0) = 1 \Rightarrow u_{11}(\tau) \\ \dot{v}_1 = u_1 - (u_1 + \kappa_1)v_1 & v_1(0) = 0 \Rightarrow v_{11}(\tau) \\ \dot{w}_1 = \lambda_1 v_1 & w_1(0) = 0 \Rightarrow w_{11}(\tau) \end{cases} \tag{28}$$

(2) Interval: $[\tau_1, \tau_2]$.

$$\begin{cases} \dot{u}_2 = \lambda_1 v_{11}(\tau) - \\ \quad -\varepsilon_2 u_2 + \varepsilon_2(u_2 + \kappa_2 - \lambda_2)v_2 & u_2(\tau_1) = w_{11}(\tau_1) \Rightarrow u_{22}(\tau) \\ \dot{v}_2 = u_2 - (u_2 + \kappa_2)v_2 & v_2(\tau_1) = 0 \quad \Rightarrow v_{22}(\tau) \\ \dot{w}_2 = \lambda_2 v_2 & w_2(\tau_1) = 0 \quad \Rightarrow w_{22}(\tau) \end{cases} \tag{29}$$

with:

$$u_{12}(\tau) = u_{11}(\tau);\ v_{12}(\tau) = v_{11}(\tau), \forall \tau \in [\tau_1, \tau_2]$$

The values for each successive interval are similarly obtained, by concatenating the solutions. So in general:

(i) Interval: $\left[\tau_{i-1}, \tau_i\right]$.

$$\begin{cases} \dot{u}_i = \lambda_{i-1} v_{i-1i-1}(\tau) - \\ \quad -\varepsilon_i u_i + \varepsilon_i(u_i + \kappa_i - \lambda_i)v_i & u_i(\tau_{i-1}) = w_{i-1i-1}(\tau_{i-1}) \Rightarrow u_{ii}(\tau) \\ \dot{v}_i = u_i - (u_i + \kappa_i)v_i & v_i(\tau_{i-1}) = 0 \quad \Rightarrow v_{ii}(\tau) \\ \dot{w}_i = \lambda_i v_i & w_i(\tau_{i-1}) = 0 \quad \Rightarrow w_{ii}(\tau) \end{cases} \tag{30}$$

with:

$$u_{ji}(\tau) = u_{jj}(\tau), v_{ji}(\tau) = v_{jj}(\tau), \forall \tau \in \left[\tau_{i-1}, \tau_i\right]$$

and so on for $i + 1, \ldots, n$. Notice how the coupling between intervals takes place in two ways: on one side, the product $w_{i-1}(\tau)$ must match the intermediate compound $u_i(\tau)$ of the next interval; on the other side, the value $v_{i-1}(\tau)$ of the enzyme-substrate complex is what allows the production of the intermediate compound $u_i(\tau)$ in the next interval.

The solution of the complete system can be described on each interval, taking into account that there are 3 laws governing the concentrations on the ith interval, $[\tau_{i-1}, \tau_i]$ (for $i = 2, \ldots, n-1$):

(a) For any $j = 1, \ldots, i-1$, the dimensionless parameters $u(\tau)$ and $v(\tau)$ satisfy:

$$u_{ji}(\tau) = u_{jj}(\tau);\ \text{ and }\ v_{ji}(\tau) = v_{jj}(\tau) \tag{31}$$

(b) The dimensionless parameters $u(\tau)$, $v(\tau)$ and $w(\tau)$ follow the laws given by (30) on the $i-$th interval.

(c) The dimensionless parameters $u(\tau)$, $v(\tau)$ and $w(\tau)$ have not been activated yet (so that their value is zero) for $j > i$:

$$u_{ji}(\tau) = v_{ji}(\tau) = w_{ji}(\tau) = 0 \ \text{ for } \ j = i + 1, \ldots, n \tag{32}$$

4 Solution of the problem

Schematically, we proceed by intervals, as follows:

(1) Interval: $[0, \tau_1]$.

In the first interval, we solve the system of ODEs with initial conditions (28) this way: as the third equation $\dot{w}_1 = \lambda_1 v_1$ is uncoupled, we only need to solve the first two. We seek functions $u(p, \tau)$ and $v(p, \tau)$ of the form:

$$u(p, \tau) = u_0(\tau) + pu_1(\tau) + p^2 u_2(\tau) + p^3 u_3(\tau) + \dots \tag{33}$$

$$v(p, \tau) = v_0(\tau) + pv_1(\tau) + p^2 v_2(\tau) + p^3 v_3(\tau) + \dots \tag{34}$$

so that two homotopies $u(\tau, p) : \Omega \times [0, 1] \to \mathbb{R}$, $v(\tau, p) : \Omega \times [0, 1] \to \mathbb{R}$ can be constructed:

$$\begin{aligned} H(u, p) &= (1 - p)\left(\varepsilon_1 u(\tau) + u'(\tau)\right) \\ &\quad + p\left(-\varepsilon_1 v(\tau)\left(\kappa_1 - \lambda_1 + u(\tau)\right) + \varepsilon_1 u(\tau) + u'(\tau)\right) \end{aligned} \tag{35}$$

$$H(v, p) = (1 - p)\left(\kappa_1 v(\tau) + v'(\tau)\right) + p\left(\kappa_1 v(\tau) + u(\tau)v(\tau) - u(\tau) + v'(\tau)\right) \tag{36}$$

By substituting Eqs. (33) and (34) into (35) and (36), and matching terms of the same power of p, we can compute the functions $u_0, u_1, u_2, \dots$ and $v_0, v_1, v_2, \dots$. We obtain the following explicitly solvable sequence of ODEs. For (35):

$$p^0 : \varepsilon_1 u_0(\tau) + u_0'(\tau) = 0 \tag{37}$$

$$\begin{aligned} &p^1 : -\varepsilon_1\kappa_1 v_0(\tau) + \varepsilon_1\lambda_1 v_0(\tau) - \varepsilon_1 u_0(\tau)v_0(\tau) + \varepsilon_1 u_1(\tau) + u_1'(\tau) = 0 \\ &p^2 : -\varepsilon_1\kappa_1 v_1(\tau) + \varepsilon_1\lambda_1 v_1(\tau) - \varepsilon_1 u_1(\tau)v_0(\tau) - \\ &\varepsilon_1 u_0(\tau)v_1(\tau) + \varepsilon_1 u_2(\tau) + u_2'(\tau) = 0 \end{aligned} \tag{38}$$

$$\begin{aligned} &p^3 : -\varepsilon_1\kappa_1 v_2(\tau) + \varepsilon_1\lambda_1 v_2(\tau) - \varepsilon_1 u_2(\tau)v_0(\tau) - \varepsilon_1 u_1(\tau)v_1(\tau) - \\ &\varepsilon_1 u_0(\tau)v_2(\tau) + \varepsilon_1 u_3(\tau) + u_3'(\tau) = 0 \end{aligned} \tag{39}$$

For (36):

$$\begin{aligned} &p^0 : \kappa_1 v_0(\tau) + v_0'(\tau) = 0 \\ &p^1 : \kappa_1 v_1(\tau) + u_0(\tau)v_0(\tau) - u_0(\tau) + v_1'(\tau) = 0 \\ &p^2 : \kappa_1 v_2(\tau) + u_1(\tau)v_0(\tau) + u_0(\tau)v_1(\tau) - u_1(\tau) + v_2'(\tau) = 0 \\ &p^3 : \kappa_1 v_3(\tau) + u_2(\tau)v_0(\tau) + u_1(\tau)v_1(\tau) + u_0(\tau)v_2(\tau) - u_2(\tau) + v_3'(\tau) = 0 \end{aligned} \tag{40}$$

Solving these EDOs, and using the boundary conditions of (28), we obtain the following results:

$$u_0(\tau) = e^{\varepsilon_1(-\tau)} \tag{41}$$

$$
\begin{aligned}
u_1(\tau) &= 0 \\
u_2(\tau) &= \frac{-e^{-2\varepsilon_1\tau}}{\kappa_1\left(\varepsilon_1-\kappa_1\right)^2}[\varepsilon_1^2\kappa_1^2\lambda_1\tau e^{\varepsilon_1\tau} - \varepsilon_1^2\kappa_1\lambda_1\tau e^{\varepsilon_1\tau} - \varepsilon_1\kappa_1\lambda_1 e^{\varepsilon_1\tau} + \\
&\quad \varepsilon_1\kappa_1\lambda_1 e^{\tau(\varepsilon_1-\kappa_1)+\varepsilon_1\tau} + +\varepsilon_1\kappa_1^3\tau\left(-e^{\varepsilon_1\tau}\right) - \kappa_1^2 e^{\varepsilon_1\tau} + \varepsilon_1^2\kappa_1^2\tau e^{\varepsilon_1\tau} + \varepsilon_1\kappa_1^2 e^{\varepsilon_1\tau} \\
&\quad - \varepsilon_1\kappa_1^2 e^{\tau(\varepsilon_1-\kappa_1)+\varepsilon_1\tau} + 2\varepsilon_1\kappa_1 e^{\varepsilon_1\tau} - \varepsilon_1\kappa_1 e^{\tau(\varepsilon_1-\kappa_1)} + \varepsilon_1^2 e^{\tau(\varepsilon_1-\kappa_1)} \\
&\quad - \varepsilon_1\kappa_1 - \varepsilon_1^2 e^{\varepsilon_1\tau} + \kappa_1^2] \\
&\quad \cdots
\end{aligned} \tag{42}
$$

and

$$
\begin{aligned}
v_0(\tau) &= 0 \\
v_1(\tau) &= -\frac{e^{-\tau(\varepsilon_1-\kappa_1)-k_1\tau}\left(e^{\tau(\varepsilon_1-\kappa_1)}-1\right)}{\kappa_1-\varepsilon_1} \\
v_2(\tau) &= -\frac{e^{-2\varepsilon_1\tau-\kappa_1\tau}\left(\varepsilon_1 e^{\varepsilon_1\tau} + \kappa_1 e^{\varepsilon_1\tau} - \kappa_1 e^{2\varepsilon_1\tau} - 2\varepsilon_1 e^{\varepsilon_1\tau} + \varepsilon_1 e^{2\varepsilon_1\tau}\right)}{\varepsilon_1\left(\kappa_1-2\varepsilon_1\right)\left(\kappa_1-\varepsilon_1\right)} \\
&\quad \cdots
\end{aligned} \tag{43}
$$

Using (7), we get:

$$
\begin{aligned}
u(\tau) &= u_0 + u_1 + u_2 + u_3 + \cdots \\
v(\tau) &= v_0 + v_1 + v_2 + v_3 + \cdots
\end{aligned} \tag{44}
$$

And, as $\dot{w}_1 = \lambda_1 v_1;\ w_1(0) = 0$, we can compute:

$$
w(\tau) = \lambda_1 \int_0^\tau v(\tau) d\tau \tag{45}
$$

We only need to revert the change of variable:

$$
u(\tau) = \frac{s(t)}{s_0};\ v(\tau) = \frac{c(t)}{e_0};\ w(\tau) = \frac{p(t)}{e_0} \tag{46}
$$

$$
s(0) = s_0, \quad e(0) = e_0, \quad c(0) = 0, \quad p(0) = 0 \tag{47}
$$

in order to, starting from $u_{11}(\tau)$, $v_{11}(\tau)$ and $w_{11}(\tau)$, obtain $s_{11}(t)$, $c_{11}(t)$ and $p_{11}(t)$. Recalling that:

$$
e(t) + c(t) = e_0 \tag{48}
$$

$$
c(t) = e_0 v(\tau) \tag{49}
$$

we have:

$$
e(t) = e_0(1 - v(\tau)) \tag{50}
$$

which gives $e_{11}(t)$.

(2) Interval: $[\tau_1, \tau_2]$.
In the second stage, the system to be solved is (29):

$$\begin{cases} \dot{u}_2 = \lambda_1 v_{11}(\tau) - \\ \quad -\varepsilon_2 u_2 + \varepsilon_2(u_2 + \kappa_2 - \lambda_2)v_2 & u_2(\tau_1) = w_{11}(\tau_1) \Rightarrow u_{22}(\tau) \\ \dot{v}_2 = u_2 - (u_2 + \kappa_2)v_2 & v_2(\tau_1) = 0 \quad \Rightarrow v_{22}(\tau) \\ \dot{w}_2 = \lambda_2 v_2 & w_2(\tau_1) = 0 \quad \Rightarrow w_{22}(\tau) \end{cases} \tag{51}$$

And we apply HPM as previously. Write:

$$u(p, \tau) = u_0(\tau) + pu_1(\tau) + p^2 u_2(\tau) + p^3 u_3(\tau) + \ldots \tag{52}$$
$$v(p, \tau) = v_0(\tau) + pv_1(\tau) + p^2 v_2(\tau) + p^3 v_3(\tau) + \ldots \tag{53}$$

And write the corresponding homotopies:

$$\begin{aligned} H(u, p) &= (1 - p)\left(\varepsilon_2 u(\tau) + u'(\tau)\right) \\ &\quad + p\left(-\varepsilon_2 v(\tau)\left(\kappa_2 - \lambda_2 + u(\tau)\right) + \varepsilon_2 u(\tau) + u'(\tau) - \lambda_1 v_{11}(\tau)\right) \end{aligned} \tag{54}$$
$$H(v, p) = (1 - p)\left(\kappa_2 v(\tau) + v'(\tau)\right) + p\left(\kappa_2 v(\tau) + u(\tau)v(\tau) - u(\tau) + v'(\tau)\right) \tag{55}$$

The same argument as above provides $s_{22}(t)$, $c_{22}(t)$, $p_{22}(t)$ and $e_{22}(t)$.

Analogously, one computes the remaining functions $s_{ii}(t)$, $c_{ii}(t)$, $p_{ii}(t)$ and $e_{ii}(t)$ on the intervals $i = 3, \ldots, n - 1$.

5 Numerical example

We are going to solve a numerical example in order to illustrate the preceding theoretical results. It is inspired on the 1-stage case of [9]. The pathway consists of two reactions each of which is catalyzed by a specific enzyme (E_i); S_1 corresponds to the substrate, S_2 is the intermediate metabolite and P denotes the product.

$$S_1 \overset{E_1}{\to} S_2 \overset{E_2}{\to} P \tag{56}$$

We are going to study three optimization problems, each with a different objective: (1) minimization of the time needed to reach a % of product. (2) Minimization of the amount of enzymes used. (3) Combined optimization of both previous variables.

Inspired by [9] we take: $\varepsilon_1 = 6$; $\kappa_1 = \lambda_1 = 0.98$; $\varepsilon_2 = 6$; $\kappa_2 = \lambda_2 = 0.98$. We shall assume, in both reactions, that: $s_0 = 1$; $e_0 = 6$ (so that $\varepsilon = \dfrac{e_0}{s_0}$). Thus, once we compute using HPM the values, $u(\tau)$, $v(\tau)$ y $w(\tau)$ one can recover $s(t)$, $c(t)$ and $p(t)$ simply recalling that:

$$s(t) = s_0 u(\tau);\ c(t) = e_0 v(\tau);\ p(t) = e_0 w(\tau) \tag{57}$$

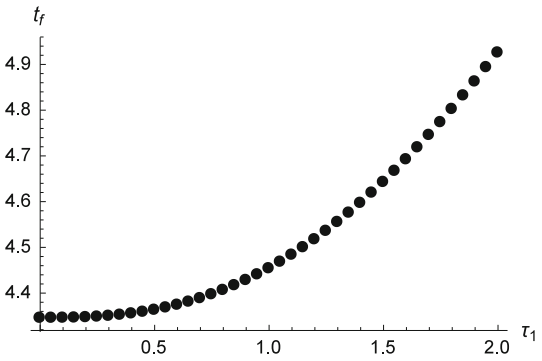

Fig. 1 Total reaction time t_f as a function of the switching time τ_1

and one also gets $e(t)$ because:

$$e(t) = e_0(1 - v(\tau)) \tag{58}$$

5.1 Case (1)

The single aim of this case is to minimize the time $t_2 = t_f$ needed to transform the substrate $s_1(t)$ into a fixed amount C_f $(0 < C_f < 1)$ of product $p(t)$. We must take into account that, after normalization, the following equality holds for all t:

$$s_1(t) + c_1(t) + s_2(t) + c_2(t) + p(t) = s_0 \tag{59}$$

As we are considering a linear pathway, we define two intervals $[0, \tau_1]$, and $[\tau_1, \tau_2]$, where τ_1 is the time when the second enzymatic reaction must begin. We are going to compute the value of τ_1 minimizing the total time t_f required to reach a specific % of the product p. We fix this value in 90% (i.e. $C_f = 0.9$). We assume an exhaustible initial substrate s_1 (i.e. the substrate is consumed during the process) and we obtain:

$$s_1(t_f) + c_1(t_f) + s_2(t_f) + c_2(t_f) = s_0\left(1 - C_f\right) \Leftrightarrow p(t_f) = s_0 C_f \tag{60}$$

Using the analytical expressions of the solutions of (28) found in the previous section, for each of the compounds, we can solve, fast and easily, by brute-force, with the desired discretization, the cases shown in Fig. 1. In this case, the optimal solution happens for $\tau_1 = 0$, which gives a final time $t_f^* = 4.34$. This means that the optimum implies starting both reactions at the same time. The optimal profiles for all the species present are shown in Fig. 2.

5.2 Case (2)

The objective now is to minimize the amount of enzymes required to transform the substrate $s_1(t)$ into a fixed rate C_f $(0 < C_f < 1)$ of the product p. Recall that:

$$e(t) = e_0(1 - v(\tau)) \tag{61}$$

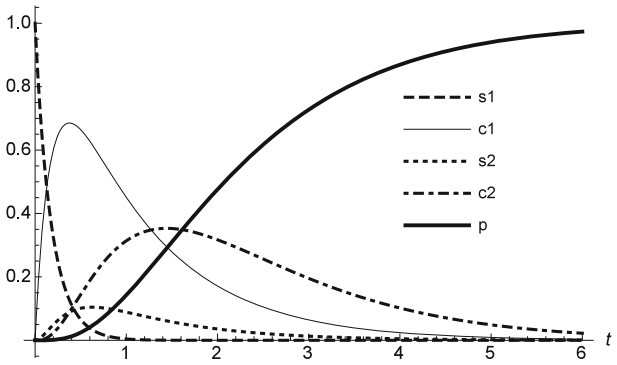

Fig. 2 Optimal profiles in case (1)

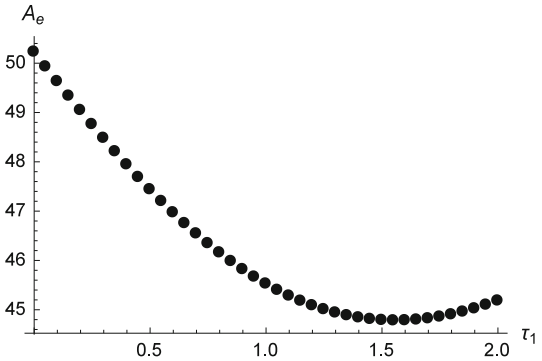

Fig. 3 Enzyme use as a function of the switching time τ_1

So that, once we compute, for each value of τ_1, the time t_f required to reach $p(t_f) = C_f$, and the profiles $e_1(t)$, $e_2(t)$, the function to be minimized in this case is:

$$A_e(\tau_1) = \int_0^{t_f} e_1(t)dt + \int_0^{t_f} e_2(t)dt$$

Using again (28) and its solutions found in the previous sections, solving for different values of τ_1, we obtain the plot in Fig. 3.

The optimal solution consists in taking $\tau_1 = 1.55(s)$. As we saw in Fig. 1, this value does not minimize the final time t_f but the combined amount of required enzymes, which takes the value $A_e = 44.80$. Thus, in this case, the optimal solution requires delaying the start of the second enzymatic reaction. The new optimal profiles are shown in Fig. 4.

5.3 Case (3)

In this last case we set as objective the combined optimization of both the two previous factors. That is, we have a multi-objective optimization problem (MOP) with non-commensurable and contradictory objectives. There is actually no single optimal

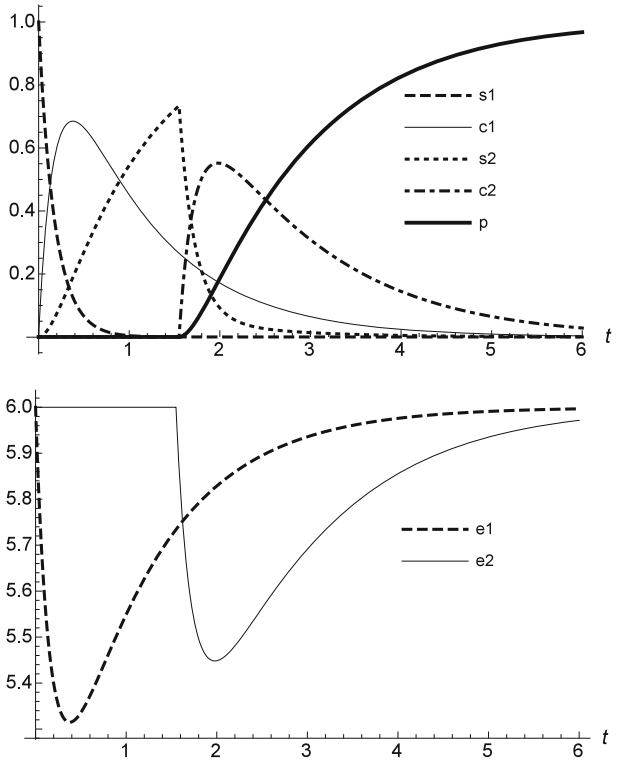

Fig. 4 Optimal profiles case (2)

solution because the exact preference or " weight" of each objective is unknown. We use the well-known Pareto optimal solution approach.

A general MOP consists of a number of objectives N to be optimized simultaneously:

$$\min F_i(x), \quad i = 1, \ldots, N \tag{62}$$

In a minimization problem, a solution x_1 dominates x_2 if the following two conditions are satisfied:

$$\begin{aligned} &\forall i \in \{1, \ldots, N\} : F_i(x_1) \leq F_i(x_2) \\ &\exists j \in \{1, \ldots, N\} : F_j(x_1) < F_j(x_2) \end{aligned} \tag{63}$$

If x_1 dominates x_2, then x_1 is called the nondominated solution within the set $\{x_1, x_2\}$. The solutions that are nondominated within the entire search space constitute the Pareto optimal set. When optimizing all objectives simultaneously, Pareto optimal solutions show the trade-offs between conflicting objective functions.

Diverse methods of generating Pareto sets exist: random sampling, the weighted sum method, the distance method, goal programming, the Pareto genetic algorith-

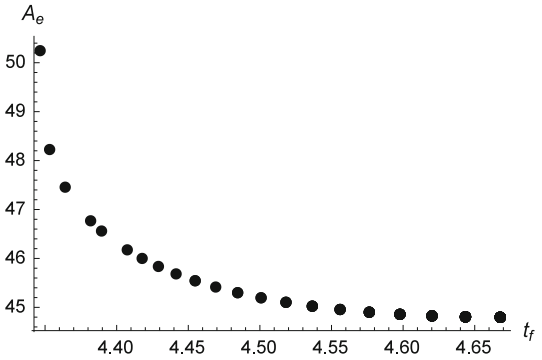

Fig. 5 Pareto front

m…The weighted sum method [20] was shown to work well with convex problems and converts the MOP into a single function optimization problem selecting scalar weights W_i and minimizing the following composite objective function:

$$U = \sum_{i=1}^{N} W_i F_i(x) \tag{64}$$

Figure 5 presents the set of compromise solutions (known as the Pareto optimal solutions set) for our two objectives: the time t_f and the total amount of enzymes A_e.

6 Notes on convergence

From the purely theoretical point of view, one should prove that the power series $u(p, \tau)$ and $v(p, \tau)$ have a radius of convergence in p strictly greater than 1 in order to obtain, at $p = 1$, the solutions $u(1, \tau)$ and $v(1, \tau)$. Focusing ourselves on the first stage, a careful development of the system (35), (36) provides the following recursive sequence of differential equations:

$$\begin{cases} u_0'(\tau) = -\epsilon_1 u_0(\tau), & u_0(0) = 1 \\ v_0'(\tau) = -\kappa_1 v_0(\tau), & v_0(0) = 0 \end{cases} \tag{65}$$

and, assuming $u_i(\tau)$, $v_i(\tau)$ are defined for $i = 0, \ldots, k-1$, then:

$$\begin{cases} u_k'(\tau) = -\epsilon_1 u_k(\tau) + \epsilon_1(\kappa_1 - \lambda_1)u_{k-1}(\tau) + \epsilon_1 \sum_{j=0}^{k-1} u_j(\tau) v_{k-1-j}(\tau) \\ v_k'(\tau) = -\kappa_1 v_k(\tau) + u_{k-1}(\tau) - \sum_{j=0}^{k-1} u_j(\tau) v_{k-1-j}(\tau) \end{cases} \tag{66}$$

with initial conditions $u_k(0) = v_k(0) = 0$ for $k > 0$. This might provide a way to study the radius of convergence.

Notice that He [13] indicates two required conditions for convergence (in the one-dimensional case), without proof: that the second derivative of the nonlinear operator N with respect to u must be small and that the norm of $L^{-1}\partial N/\partial u$ must be smaller

than one. These do not translate clearly to the two-dimensional case and, furthermore, our linear part is non-inversible $\left(\begin{smallmatrix} -\epsilon & 0 \\ 1 & 0 \end{smallmatrix}\right)$.

In [21], the authors state a result (Theorem 3.2) which provides a condition for convergence. However, it is just the definition of radius of convergence less than 1 for a power series, so that it is practically useless.

When dealing with convergence, each problem is usually studied case by case, without recourse to a general argument. For example, He in [13], studies the Lighthill equation or the Duffing equation and does not provide a strict proof of convergence in the second case (the first one gives the solution trivially) and proceeds similarly in [14]. The same can be said of Ayati and Biazar's study of the Lane–Emdem equation in [21].

Returning to our study, we have been unable to obtain a definitive result using the recursion given by (65) and (66). However, we have carried out explicit numerical computations for both the first and second stages and obtained a reasonable suggestion of convergence for u_k and v_k. Specifically, for case (2) (i.e. Sect. 5.2), and computing, for the interval $\tau \in [0, 6]$ the maximum values of $M_{1,k} = \max(|u_{1,k}(\tau)|)$, $N_{1,k} = \max(|v_{1,k}(\tau)|)$ for the first stage, and $M_{2,k} = \max(|u_{2,k}(\tau)|)$, $N_{2,k} = \max(|v_{2,k}(\tau)|)$ for $\tau \in [1.55, 6]$ for the second stage, we obtain the following numerical recursion for $k > 20$ (up to $k = 50$) (see Annex I for a complete dataset):

$$\begin{array}{ll} M_{1,k-1}/M_{1,k} > 2, & N_{1,k-1}/N_{1,k} > 2 \\ M_{2,k-1}/M_{2,k} > 2, & N_{2,k-1}/N_{2,k} > 2. \end{array} \tag{67}$$

which is a strong evidence supporting that the radius of convergence is strictly greater than 1.

7 Conclusions

Due to the difficulties in solving the nonlinear differential equations that appear in enzyme kinetics, some recent advanced analytical techniques are being used. The most popular and useful model is the Michaelis–Menten form. In this paper we obtain an analytic approximate solution using the Homotopy Perturbation Method, which presents important features for solving engineering problems: applicability, accuracy, efficiency. It is very effective and simple and, in this case, only a few iterations are needed to find an approximate solution. Our main contribution is the generalization of previous works to the case of a linear pathway of multiple reactions. We show how, using this technique, we can solve problems with different objectives and avoid some of the deficiencies of the weighted sum method for generating Pareto sets.

8 Annex I: dataset

Table 1 shows, as explained in Eq. (67), the list of the maxima $M_{1,k} = \max |u_{1,k}(\tau)|$, $N_{1,k} = |v_{1,k}(\tau)|$, for $\tau \in [0, 6]$, corresponding to the first stage of case (2) (i.e. Sect. 5.2).

Table 1 Convergence for the first stage of reaction (2)

k	$M_{1,k}$	$M_{1,k}/M_{1,k+1}$	$N_{1,k}$	$N_{1,k}/N_{1,k+1}$
1	0.	0.	0.117011	13.9644
2	0.0246043	20.2154	−0.00837922	1.04485
3	−0.00121711	0.451725	0.00801958	5.63712
4	0.00269435	8.00936	−0.00142264	1.31365
5	−0.000336401	0.854245	0.00108297	3.87805
6	0.000393799	4.92861	−0.000279256	1.54625
7	−0.0000799005	1.19953	0.000180602	3.11263
8	0.0000666097	3.65603	−0.0000580222	1.72591
9	−0.0000182191	1.4721	0.0000336183	2.70605
10	0.0000123763	3.0128	−0.0000124234	1.85098
11	-4.10791×10^{-6}	1.67325	6.71179×10^{-6}	2.47233
12	2.45504×10^{-6}	2.64462	-2.71476×10^{-6}	1.93899
13	-9.28318×10^{-7}	1.80455	1.40009×10^{-6}	2.28468
14	5.14432×10^{-7}	2.44277	-6.12817×10^{-7}	1.98186
15	-2.10594×10^{-7}	1.90129	3.09214×10^{-7}	2.32739
16	1.10764×10^{-7}	2.30036	-1.32859×10^{-7}	2.16034
17	-4.81506×10^{-8}	1.96221	6.14988×10^{-8}	2.18003
18	2.4539×10^{-8}	2.21224	-2.82101×10^{-8}	2.03218
19	-1.10923×10^{-8}	2.00275	1.38817×10^{-8}	2.1167
20	5.53855×10^{-9}	2.1556	-6.55815×10^{-9}	2.03023
21	-2.56938×10^{-9}	2.02538	3.23026×10^{-9}	2.08341
22	1.26859×10^{-9}	2.12009	-1.55046×10^{-9}	2.03139
23	-5.98368×10^{-10}	2.04016	7.63252×10^{-10}	2.06613
24	2.93295×10^{-10}	2.09733	-3.69411×10^{-10}	2.03463
25	-1.39842×10^{-10}	2.04731	1.81562×10^{-10}	2.05704
26	6.83054×10^{-11}	2.08076	-8.82637×10^{-11}	2.0383
27	-3.28271×10^{-11}	2.0496	4.33027×10^{-11}	2.05225
28	1.60163×10^{-11}	2.06957	-2.11001×10^{-11}	2.04139
29	-7.73899×10^{-12}	2.05015	1.03362×10^{-11}	2.04977
30	3.77484×10^{-12}	2.06154	-5.0426×10^{-12}	2.0436
31	-1.83107×10^{-12}	2.049	2.46751×10^{-12}	2.04844
32	8.93645×10^{-13}	2.05472	-1.20458×10^{-12}	2.04495
33	-4.34923×10^{-13}	2.0465	5.89049×10^{-13}	2.04761
34	2.12521×10^{-13}	2.04848	-2.87676×10^{-13}	2.04555
35	-1.03745×10^{-13}	2.04316	1.40635×10^{-13}	2.04691
36	5.0777×10^{-14}	2.04438	-6.87061×10^{-14}	2.04562
37	-2.48373×10^{-14}	2.04028	3.35869×10^{-14}	2.04622
38	1.21735×10^{-14}	2.04041	-1.64141×10^{-14}	2.04536

Table 1 continued

k	$M_{1,k}$	$M_{1,k}/M_{1,k+1}$	$N_{1,k}$	$N_{1,k}/N_{1,k+1}$
39	-5.96618×10^{-15}	2.03725	8.02507×10^{-15}	2.04551
40	2.92855×10^{-15}	2.03651	-3.92327×10^{-15}	2.04485
41	-1.43802×10^{-15}	2.03382	1.91861×10^{-15}	2.04474
42	7.07055×10^{-16}	2.03289	-9.38312×10^{-16}	2.04419
43	-3.47808×10^{-16}	2.03083	4.59015×10^{-16}	2.04392
44	1.71264×10^{-16}	2.02986	-2.24576×10^{-16}	2.04339
45	-8.43722×10^{-17}	2.02819	1.09904×10^{-16}	2.04303
46	4.15997×10^{-17}	2.02719	-5.37944×10^{-17}	2.04252
47	-2.05208×10^{-17}	2.02576	2.63373×10^{-17}	2.04209
48	1.013×10^{-17}	2.02473	-1.28972×10^{-17}	2.04158
49	-5.00311×10^{-18}	2.02342	6.31729×10^{-18}	2.04111

Table 2 shows the same data for the second stage of the same reaction, $M_{2,k} = \max |u_{2,k}(\tau)|$, $N_{2,k} = |v_{2,k}(\tau)|$, for $\tau \in [1.55, 6]$.

Table 2 Convergence for the first stage of reaction (2)

k	$M_{2,k}$	$M_{2,k}/M_{2,k+1}$	$N_{2,k}$	$N_{2,k}/N_{2,k+1}$
1	0.0304882	2.29952	0.0858949	6.24724
2	0.0132585	5.46158	0.0137492	4.43821
3	0.0024276	2.2808	0.00309793	4.12129
4	0.00106436	3.7561	0.000751689	2.5851
5	0.00028337	2.48966	0.000290778	3.85704
6	0.000113819	3.00331	0.0000753888	2.17118
7	0.0000378976	2.64415	0.0000347225	3.2215
8	0.0000143326	2.68294	0.0000107784	2.44195
9	5.34213×10^{-6}	2.66912	4.41384×10^{-6}	2.75776
10	2.00146×10^{-6}	2.56392	1.60051×10^{-6}	2.57003
11	7.80625×10^{-7}	2.63821	6.22761×10^{-7}	2.60893
12	2.95892×10^{-7}	2.53795	2.38704×10^{-7}	2.70646
13	1.16587×10^{-7}	2.58961	8.81979×10^{-8}	2.4843
14	4.50212×10^{-8}	2.53047	3.55021×10^{-8}	2.50592
15	1.77916×10^{-8}	2.55744	1.41673×10^{-8}	2.59194
16	6.95679×10^{-9}	2.51678	5.4659×10^{-9}	2.50813
17	2.76416×10^{-9}	2.53826	2.17927×10^{-9}	2.5365
18	1.089×10^{-9}	2.50728	8.59162×10^{-10}	2.5098
19	4.34336×10^{-10}	2.51983	3.42322×10^{-10}	2.51753

Table 2 continued

k	$M_{2,k}$	$M_{2,k}/M_{2,k+1}$	$N_{2,k}$	$N_{2,k}/N_{2,k+1}$
20	1.72367×10^{-10}	2.50101	1.35976×10^{-10}	2.49795
21	6.8919×10^{-11}	2.50515	5.44347×10^{-11}	2.49685
22	2.7511×10^{-11}	2.49285	2.18013×10^{-11}	2.48612
23	1.1036×10^{-11}	2.49493	8.76923×10^{-12}	2.49188
24	4.42336×10^{-12}	2.48568	3.51912×10^{-12}	2.47829
25	1.77954×10^{-12}	2.4856	1.41998×10^{-12}	2.4803
26	7.15939×10^{-13}	2.47946	5.72501×10^{-13}	2.47226
27	2.88748×10^{-13}	2.47912	2.3157×10^{-13}	2.46889
28	1.16472×10^{-13}	2.47422	9.3795×10^{-14}	2.46142
29	4.70741×10^{-14}	2.4727	3.81061×10^{-14}	2.45846
30	1.90375×10^{-14}	2.46938	1.55×10^{-14}	2.45322
31	7.70943×10^{-15}	2.46821	6.31822×10^{-15}	2.45152
32	3.12349×10^{-15}	2.46574	2.57727×10^{-15}	2.44807
33	1.26675×10^{-15}	2.46391	1.05278×10^{-15}	2.44678
34	5.14122×10^{-16}	2.46151	4.3027×10^{-16}	2.44471
35	2.08864×10^{-16}	2.4601	1.76001×10^{-16}	2.44385
36	8.49008×10^{-17}	2.45839	7.20179×10^{-17}	2.44256
37	3.45351×10^{-17}	2.45717	2.94846×10^{-17}	2.44206
38	1.40548×10^{-17}	2.45541	1.20737×10^{-17}	2.44131
39	5.72401×10^{-18}	2.45376	4.94557×10^{-18}	2.60063
40	2.33275×10^{-18}	2.45218	1.90168×10^{-18}	2.28549
41	9.51297×10^{-19}	2.45092	8.32069×10^{-19}	2.44293
42	3.88139×10^{-19}	2.44966	3.40604×10^{-19}	2.62942
43	1.58446×10^{-19}	2.44855	1.29535×10^{-19}	2.42252
44	6.47103×10^{-20}	2.4435	5.34713×10^{-20}	2.27777
45	2.64826×10^{-20}	2.43642	2.34753×10^{-20}	2.46555
46	1.08695×10^{-20}	2.4495	9.52131×10^{-21}	2.43885
47	4.43742×10^{-21}	2.41733	3.90402×10^{-21}	2.60246
48	1.83567×10^{-21}	2.43314	1.50013×10^{-21}	2.27885
49	7.54443×10^{-22}	2.45961	6.58281×10^{-22}	2.44056

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